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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,889	06/04/2007	Peter Svete	33668US-PCT	3731

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EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,889	SVETE ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/10/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 18- 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 18- 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 and 18-19 are pending. Receipt and consideration of Applicants' amended claim set and remarks/arguments mailed on 07/10/2008 is acknowledged. Claims 1,9, 10 and 18 are amended.

Applicants' arguments, filed 7/10/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 102 (e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8 are rejected under 35 U.S.C. 102(e) as being anticipated in Antoncic et al. (US 7271269) **is maintained** for reasons of record which has been restated below.

Antoncic discloses a potassium salt of losartan characterized by a powder X-ray diffraction pattern with peaks at about 2θ 6.9, 13.8, 20.6, 24.8, 28.7, 29.2° (Form X)

(column 14, lines 14-17) and pharmaceutical composition containing polymorphic forms of losartan specifically the form exhibiting strongest diffractions at around 2θ 6.9, 13.8, 20.6, 24.8, 28.7, 29.2° (Form X) (column 15, lines 41-42 and lines 63-65). This reads on instant claims 1, 2 and 4.

Antoncic discloses an aspect of their invention where in the pharmaceutical active ingredient of the composition is the amorphous form of losartan (column 17, lines 11-16) (reads on instant claim 3) and film coated tablet formulations of potassium salt of losartan with suitable excipients (column 16, lines 12-21) (reads on instant claim 5). The following examples 52a and 52b disclosed by Antoncic describe the coated tablet formulation of polymorphic forms of potassium salt of losartan. Excipients claimed in the instant claim 1, 6-8 are indicated by arrows in the examples.

EXAMPLE 52a

(Film Coated Tablets)
Composition of a tablet

core	
Losartan potassium	100.000 mg
Silicified Microcrystalline Cellulose	199.200 mg
Croscarmellose Sodium	16.800 mg
Silica Colloidalis Anhydrica	3.200 mg
Magnesium stearate	1.800 mg
coating	
Hydroxypropylcellulose	4.560 mg
Ethylcellulose	8.540 mg
Triethyl citrate	2.660 mg
Titanium dioxide	1.080 mg
Ferric oxide red	0.020 mg
Talc	2.660 mg
Weight	346.000 mg
*Ethanol	120.000 mg
**Talc	0.220 mg

*Ethanol is removed during the process
**Talc is not included into the coating polishing agent

EXAMPLE 52b

(Film Coated Tablets)

Composition of a Tablet

core	
Losartan potassium	100.000 mg
Silicified Microcrystalline Cellulose	199.200 mg
Croscarmellose Sodium	16.000 mg
Silica Colloidalis Anhydrica	3.200 mg
Magnesium stearate	1.600 mg
coating	
Hydroxypropylcellulose	15.900 mg
Stearic acid	2.100 mg
Triethyl citrate	3.500 mg
Titanium dioxide	1.080 mg
Ferric oxide red	3.010 mg
Talc	1.170 mg
Weight	336.000 mg
*Ethanol	140.000 mg
*Talc	0.210 mg

*Ethanol is removed during the process
*Talc is not included into coating, polishing agent

In example 52a above calculation of % weight of ethyl cellulose by total weight of the pharmaceutical compositions yields a value of 0.13% and in example 52b calculation of % weight of the stearic acid by total weight of the pharmaceutical composition yields a value of 0.2%. Both these values are well within the range claimed in instant claim 6. Calculations of % weight of anhydrous silica (Silica colloidalis Anhydrica) in examples 52a and 52b above yields a value of about 1% which is within the range claimed in claim 7-8 of the instant application.

Applicant's arguments:

Applicants present the following arguments in traversing the102 (e) rejections set forth in the previous office action:

Amendment of claim 1 in the amended claims filed on 07/10/2008 includes a proviso at the end of the claim " wherein the stabilizing substance is present in an amount from about 1% to about 10 % by weight of the pharmaceutical composition". Applicants argue that the last proviso about the weight percent of the stabilizing substance is new

to Claim 1 and that It avoids any alleged anticipation of Antoncic. This is because Antoncic does not disclose the use of a stabilizing substance in the range of from about 1% to about 10 % by weight of the pharmaceutical composition. Applicant provides a table of calculations where they show that the stabilizing substance described in Examples 52a and 52b are actually said to be present in an amount of 0.95 wt%.

Response to the argument:

Applicant's arguments filed on 07/10/08 have been fully considered, but are not found to be persuasive.

Although the weight calculations of the stabilizer in examples 52a and 52b brings the final concentration to 0.95% by weight. The "about 1-10%" term in the instant claim 1 renders 0.95% anticipatory. In the absence of the actual definition of the term "about" and the ranges encompassed by it, 0.95% is well within the margin of error for 1% and can be rounded to 1%. Accordingly, Antoncic anticipates instant claims 1-8 and the rejection is maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Rejection 1

The rejection of claims 1-8 and 18-19 of the instant application under 35 U.S.C. 103(a) as being unpatentable over Dolitzky et al (US 2004/0006237) and Campbell et al (US 5608075) and Antoncic et.al (US 7271269)..**is maintained** for reasons of record which has been restated below.

Dolitzky teaches polymorphic forms of amorphous losartan potassium (page 1, section (0002) and (0003)) specified in instant claims 1-3. Dolitzky also teaches a pharmaceutical composition containing polymorphic forms of amorphous losartan potassium along with one or more suggested excepients which include colloidal silicon dioxide (0080-0081) specified in instant claim 1. Additionally Dolitzky teaches the method of treating hypertension in a patient suffering from hypertension by administering to a patient a dosage form of losartan potassium (claim 8 and claim 26, 43) specified in instant claims 18-19.

Campbell teaches the mechanism of action of polymorphic forms of Losartan, in that they are known to inhibit the action of the octapeptide hormone angiotensin II and are useful therefore in alleviating angiotensin induced hypertension. He also teaches

that administration of losartan with a non-steroidal anti-inflammatory drug (NSAID) can prevent renal failure which sometimes results from administration of a NSAID (column 1, lines 9-42). This reads on instant claims 18-19.

Antoncic teaches pharmaceutical compositions comprising of polymorphic forms potassium salt of losartan with pharmaceutical excipients which includes colloidal anhydrous silica (see above examples 52a and 52b) as described in the U.S 35 102 (e) rejection above

What Dolizky, Campbell and Antoncic do not teach is the specific use of a stabilizing substance such as anhydrous silicon dioxide in a pharmaceutical composition to stabilize a polymorphic form of potassium salt of losartan from degradation. Applicant identifies colloidal silicon dioxide as having stabilizing property to stabilize polymorphic forms of potassium salt of Losartan. Stabilizing effect is a property of anhydrous colloidal silicon dioxide. A component and its property cannot be separated. Silicon dioxide when present in compositions as taught by Antoncic (see above examples 52a and 52b) will inherently exhibit its stabilizing property.

Applicant's arguments:

None of the cited references, Dolitzky, Campbell, or Antoncic discloses, teach or suggest a composition or method comprising a stabilizing substance present in an amount from about 1% to about 10 % by weight of the pharmaceutical composition. Dolitzky does not give any disclosure of any amounts of any excipients. Campbell discloses the preparation of a tablet, however, the amounts do not fall within the present

claim scope . Also, Antoncic is not citable against the claims in this case due to application of 35 U.S.C. § 103(c). Both this case and Antoncic are owned by the same entity or subject to an obligation to assign to the same entity (LEK Pharmaceuticals) and Antoncic is cited as prior art under 102(e). Thus, no part of Antoncic may properly be cited against the present claims, which plainly and undisputedly patentably distinguish over Dolitsky and Campbell.

Response to the Argument:

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For instance, applicant argues that Dolitzky does not disclose any amounts of any excepients, however, this is taught by Antoncic and applicant argues that Campbell's concentrations in his formulation does not fall within the claimed ranges, again, this is taught by Antoncic. The concentration of the stabilizer recited by Antoncic falls with the range claimed in the instant application and one of ordinary skill in the art would be motivated to try concentrations close to the claimed range to come up with the tolerance range of the ingredients Accordingly, the three references when taken together renders the instant claims obvious.

In response to the argument that Antoncic is not citable against the claims in this case due to application of 35 U.S.C. § 103(c). Both this case and Antoncic are owned

by the same entity or subject to an obligation to assign to the same entity (LEK Pharmaceuticals).

Examiner agrees with the Applicant that the Antoncic patent and the instant application are owned by the same entity, for the reference to be disqualified from consideration due to application of 35 U.S.C. § 103(c). According to MPEP section 706.02,

Effective November 29, 1999, subject matter which was prior art under former 35U.S.C. 103 via 35 U.S.C. 102(e) was disqualified as prior art against the claimed invention if that subject matter **and the claimed invention "were, at the time the invention was made, owned by the same person** or subject to an obligation of assignment to the same person."

Examiner would like to point out that the applicant has not made any references in his arguments about the timing of the invention and therefore the argument is not persuasive. The rejection is accordingly maintained.

Rejection 2

The rejection of claims 1-3 and 18-19 of the instant application under 35 U.S.C. 103(a) as being unpatentable Antoncic et.al (US 7271269) in view of Bharatarajan et.al. (US 2006/0177498) **is maintained** for reasons of record which has been restated below.

Antoncic teaches pharmaceutical compositions comprising of potassium salt of losartan with pharmaceutical excipients as described in the above rejection.

What Antoncic does not teach is the exact type of finely divided Silicon dioxide as Syloid™ claimed in instant application.

This deficiency is cured by Bharatarajan, who teaches the use Syloid AL-1 claimed in Instant application as one of the suitable excipients with low moisture content that prohibit uptake of moisture and provide the effect of increased stability of formulations with low water contents excipients (0016, 0025-0026). Bharatarajan also provides Example 3 (0036) where Syloid AL-1 is used in a formulation of ramipril. The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because it would have been *prima facie* obvious to the skilled artisan to try different types of excipients and known moisture absorbing materials to achieve the desired level of stabilization in the composition. Selection of excipients and the amounts to be used can be readily determined by one of ordinary skilled in the arts based upon experience and consideration of standard procedures and reference work in the field. One would be motivated to do so to achieve the most stable and effective pharmaceutical composition.

The experimental data disclosed by the applicant (Specification pages 11-15) to demonstrate the properties of the claimed composition is noted and acknowledged. Data presented demonstrates the intrinsic stabilizing property of anhydrous finely divided silicon dioxide and cannot be used to overcome the instant rejection.

Applicant's arguments:

Antoncic is not properly citable against the present claims according to the dictates of 35 U.S.C. § 103(c) but, in any event, it does not disclose the claimed range of stabilizing substance. In fact, Antoncic discloses using only a very small amount of what is said to be a stabilizing substance. (See the table presented above). On the other hand, Bharatarajan is not directed to the same active ingredient as Antoncic, and therefore would not be "obviously" combined with Antoncic in any event. One of skill in the art would not consult literature describing a completely different active ingredient. Further, there would be no motivation to do so after reading Antoncic. Antoncic does not indicate that the disclosed formulations shown in Examples 52a and 52b would be "unstable." It is only after considering Applicant's present specification that one would be led to methods to stabilize the crystallinity of the claimed active ingredient susceptible to degradation or interconversion into other polymorph forms. The mere fact that Bharatarajan discloses stabilizing a completely different pharmaceutical (i.e., ramipril) does not provide a motivation to stabilize according to Applicants' claims, especially since Antoncic would not be in the picture by virtue of § 103 (c).

Response to the Argument:

Please see the response to 103 rejection 1 above for applicant's argument with reference to the Antoncic reference being not properly citable against the present claims according to the dictates of 35 U.S.C. § 103(c and for the argument that the claimed range of stabilizing substance is not disclosed. In response to applicant's argument that Bharatharajan is nonanalogous art as it does not teach the same active ingredient, it

has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the two references are indeed analogous because although structurally different, both losartan and armorial are used to treat hypertension and through different mechanisms of action, ultimately act by suppressing angiotensin II activity. Losartan is a selective, competitive angiotensin II receptor type 1 antagonist and reduces the end organ responses to angiotensin II. Ramipril is an angiotensin converting enzyme (ACE) inhibitor which lowers the production of angiotensin II. Both references are drawn towards active ingredient used in the treatment of same indications, and search for losartan as an antihypertensive will result in art referencing ramipril. Accordingly, one of ordinary skill in the art will be motivated to use the stabilizing agent taught by Baratharajan in the pharmaceutical composition of Antoncic.

Conclusion

Claims 1-10 and 18-19 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614